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A systematic review of semicarbazones as an anticonvulsant agent

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ABSTRACT

Anticonvulsants are a diverse group of pharmaceuticals used in the treatment of epileptic seizures. The goal of an anticonvulsant is to suppress the rapid and excessive firing of neurons that start a seizure. The use of current antiepileptic drugs has been questioned due to the non selectivity of the drugs and the undesirable side effects posed by them. This lead to the search for antiepileptic compounds with more selective activity and lower toxicity continues to be an area of investigation in medicinal chemistry. Semicarbazones are compounds which are synthesized by the condensation of semicarbazide and aldehydes/ketones. The literature survey revealed that semicarbazones had been emerged as a compound with broad range of activities including anticonvulsant, antitubercular, anticancer and antimicrobial activity. In this review chemistry and anticonvulsant activity of semicarbazone analogues are discussed.

Introduction

Epilepsy is a complex and chronic neurological disorder characterized by the unpredictable recurrence of unprovoked seizures and is associated with a high degree of morbidity and mortality. A seizure is the clinical expression of abnormal neuronal firing within the brain that occurs with or without the loss of consciousness. Both genders are affected equally, but the incidence of epilepsy is highest during childhood, reaches a plateau until the age of 65, and increases thereafter [1]. Approximately 2.5 million people [2], including 340,000 children in the United States and about 45- 100 million people worldwide, suffer from epilepsy and its sequelae [3]. Prior to 1990, the medical treatment of patient with epilepsy was accomplished by using one or a combination of classical [4] antiepileptic drugs (AEDs) such as phenytoin, carbamazepine, and valproate. All these established drugs have failed to control seizures in 25 – 30% patients and are proved to cause intolerable adverse effects (like neurotoxicity, fatal idiosyncratic disorders, etc.) in patients receiving either monotherapy or polytherapy. In the past decade, a group of new AEDs, including felbamate, gabapentin, lamotrigine, oxcarbazepine, and some others, have been made available to patients with epilepsy, but yet not all of them have had their seizures controlled or their adverse effects completely eliminated. Recently, several investigational AEDs, including ganoxolone, ramacemide, rufinamide, etc. [5], have been put into clinical trials and only limited data on their efficacy and safety against a particular seizure type are available to date. Although the diagnosis of seizure type and treatments are complicated, the therapy of patients with epilepsy has been accomplished in current clinical practice by administering one or a combination of classical and new epileptic drugs; however, they still suffer from unwanted side effects like sedation, which stimulates the search for safer, better, and more effective AEDs.

Unverferth *et al.* [7] suggested a pharmacophore model for structurally different anticonvulsants containing aryl rings and electron donor and hydrogen bond donor/acceptor functions. During the last fifteen years, semicarbazones emerged as novel anticonvulsant entities in the laboratories of Dimmock [8, 9] and Pandeya [10, 11].

Table 1: Major side effects of commonly used anticonvulsants [6]

DRUG	SIDE EFFECTS
Phenobarbital	Dizziness, lethargy, hypotension, apnea, megaloblastic anemia, Liver damage and so on.
Phenytoin	Nausea, skin rashes blood dyscrasias, hyperglycemia cardiac arrhythmias and so on.
Trimethadone	Drowsiness, G.I.distress, vertigo, diplopia, epistaxis, alopecia, nephrosis, foetal malformation and so on.
Ethosuximide	G.I. distress, euphoria, confusion, myopia, urticaria, vaginal bleeding and so on.
Carbamazepine	Dizziness, ataxia, drowsiness, hallucinations, dermatologic sweating, genitourinary albuminaria, hypotension, liver dysfunction and so on.
Primidone	Lethargy, ataxia, vertigo, irritability, severe skin rashes, lymphadenopathy, impotence, visual disturbances, lupus like reactions and so on.
Sodium valproate	Nausea, vomiting, indigestion, sedation, abdominal cramps, fetal hepatic failure, alopecia, irregular menses, acute pancreases, blood dyscrasias and so on.
Lamotrigine	Dizziness, ataxia, blurred vision, vomiting, skin rashes, Stevens Johnson syndrome, disseminated intravascular coagulation

The structural requirements in the semicarbazone series are: a lipophilic aryl ring, a distal aryl ring, a hydrogen-bonding domain (HBD) and an electron donor acceptor system (Figure 1.). The lipophilic aryl ring with chloro, bromo or nitro groups has been found to be essential for anticonvulsant activity.

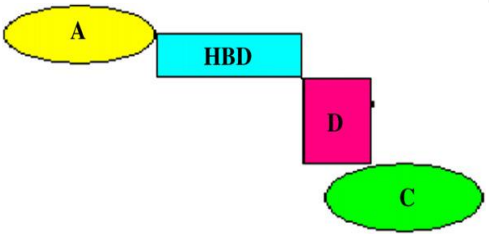

Fig 1. Proposed pharmacophore model for anticonvulsant activity: (A) hydrophobic aryl ring; (HBD) hydrogen-bonding domain; (C) distal aryl ring; (D) electron donor acceptor group

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Semicarbazones

Chemistry of Semicarbazones

Semicarbazones are among the most relevant nitrogen-oxygen donor ligands (Figure 2.).

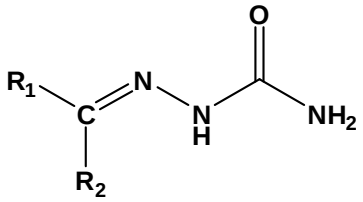
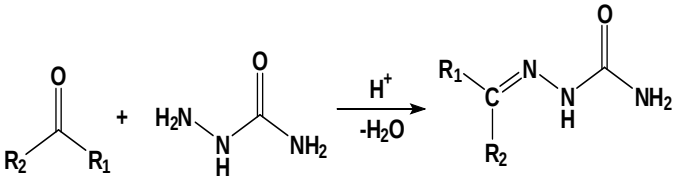


Fig. 2. General Structure of semicarbazone analogues

Semicarbazones are the Schiff bases, usually obtained by the condensation of semicarbazide with suitable aldehydes and ketones **(Scheme 1.).**



Scheme 1. Method of Synthesis of semicarbazone

According to IUPAC recommendations, semicarbazones may be named by adding the class name 'semicarbazone' after the name of the condensed aldehyde or ketone. It is usual also to include in this class derivatives with substituents on the amide nitrogen. The numbering scheme shown in the Figure 3. is in accordance with IUPAC system.

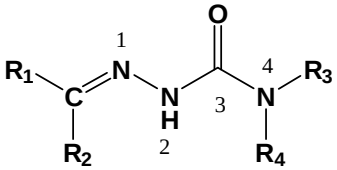
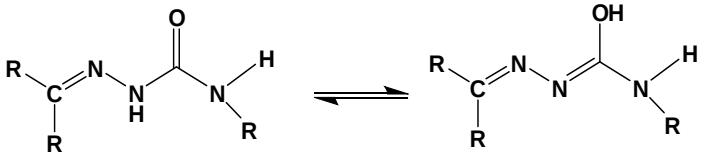


Fig. 3. Numbering scheme of the semicarbazone.

An interesting attribute of the semicarbazones is that in the solid state, they predominantly exist in the keto form, whereas in solution state, they exhibit a keto-enol tautomerism (Figure 4.). Keto form acts as a neutral bidentate ligand and the enol form can deprotonate and serve as monoanionic bidentate ligand in metal complexes. Thus semicarbazones are versatile ligands in both neutral and anionic forms.

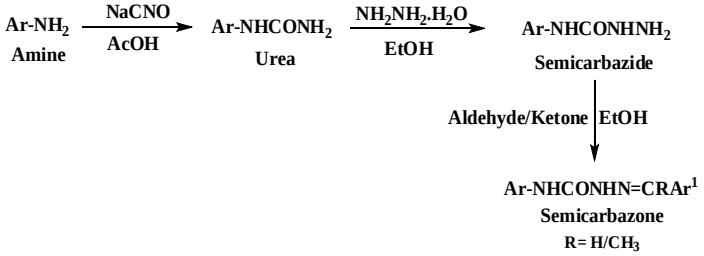


keto (A) **enol (B)**

Fig. 4. Keto-enol tautomerism of semicarbazones

General method for the synthesis of semicarbazone analogues

The general method for the synthesis of semicarbazone analogues is presented in Scheme 2.



Scheme 2. General method for the synthesis of semicarbazone analogues.

Spectral studies on semicarbazones

Infrared

The carbonyl stretching C=O vibration [12, 13] is expected in the region 1715-1680 cm^{-1} in the IR spectrum. The δ C=O in-plane deformation and the out-of-plane deformation γ C=O are expected in the regions 625 ± 70 and 540 ± 80 cm^{-1} respectively [12]. According to Socrates [14], the υC=N for semicarbazones is expected in the region 1655-1640 cm^{-1} in IR spectrum. A perusal through literature shows that C=O and C=N stretching modes are reported at 1668, 1671 and 1613, 1602, 1719, 1600 [15, 16], 1669, 1618 [17], 1680, 1586 [18], and at 1682, 1574 cm^{-1} for semicarbazone derivatives [19]. The NH stretching vibration [12] appears as a strong and broad band in the region 3390 ± 60 cm^{-1}. The C-N stretching vibration [12] coupled with the δNH, is active in the region 1275 ± 55 cm^{-1}. The vibrations of the CH_2 group, the asymmetric stretch, υasCH_2, symmetric stretch υsCH_2, scissoring vibration δCH_2 and wagging vibration ωCH_2 appear in the regions 3000 ± 50, 2965 ± 30, 1455 ± 55 and 1350 ± 85 cm^{-1}, respectively [12, 20]. The rocking mode [12] is expected in the range 895 ± 85 cm^{-1}. The NH_2 asymmetric stretching vibrations [12] give rise to a strong band in the region 3390 ± 60 cm^{-1} and the symmetric NH_2 stretching in the region 3210 ± 60 cm^{-1} with a somewhat weaker intensity.

Geometrical parameters

The NN bond lengths are reported as 1.3782-1.389 [21], 1.3866 [22], 1.3894 [23], 1.3966 [24], 1.3796 [25], 1.3675 [26], 1.367 [27], 1.36 [28], and 1.369 Å [29].

^{1}H NMR

Dimmock *et al.* [30] studied the ^{1}H NMR spectra of 1-(4-fluorophenyl)ethanone semicarbazone in DMSO-d6; the chemical shift and spin coupling constants are given. The1-(4 fluorophenyl)ethanone semicarbazone (Figure 5.) have five characteristic peaks in the NMR spectrum, H(2',6'-H, Aromatic) appears as a triplet at δ 7.18, H(3',5'-H, Aromatic) appears as a triplet at 7.90 ppm, H(CH_3) appears as a singlet at δ 2.20, (H)NH appears as a singlet at δ 9.39 and (H)NH_2 appears as a singlet at δ 6.54.

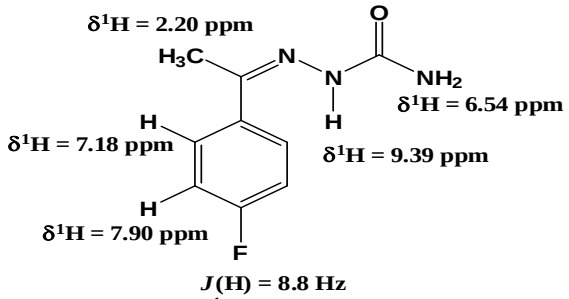


Fig. 5. Representative ^{1}H NMR data of 1-(4-fluorophenyl) ethanone semicarbazone.

^{13}C NMR

Dimmock *et al.* [30] studied the ^{13}C NMR spectra of 1-(4-fluorophenyl)ethanone semicarbazone in DMSO-d6; the chemical shift and spin coupling constants are given in the Figure 6.

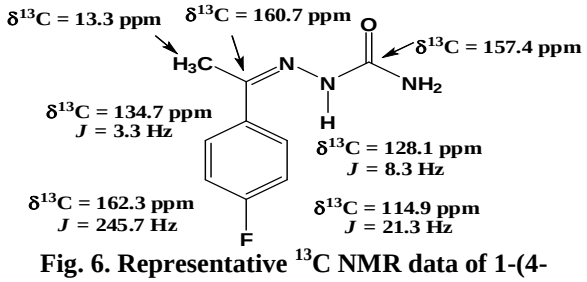


Fig. 6. Representative ^{13}C NMR data of 1-(4-fluorophenyl)ethanone semicarbazone.

Mass spectral studies

Berdyshev [31] reported the mass spectra of fatty aldehyde semicarbazone derivatives (Figure 7.).

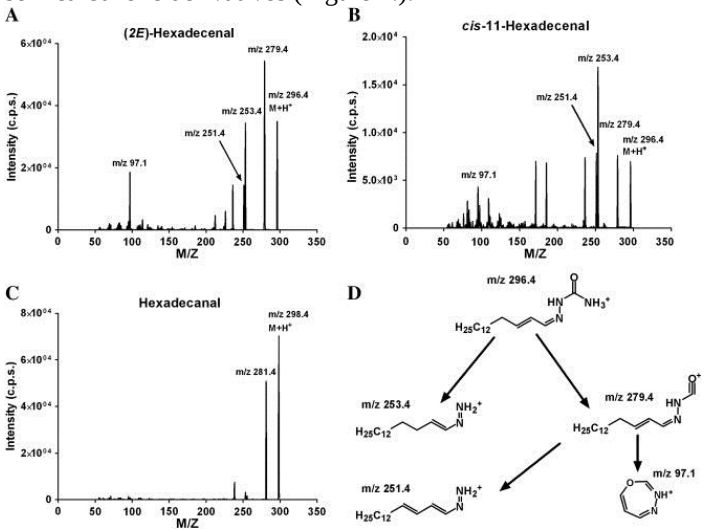


Fig. 7. Positive product ion mass spectra of fatty aldehyde semicarbazone derivatives. (A) (2E)-Hexadecenal semicarbazone product ions. (B) *cis*-11-Hexadecenal semicarbazone product ions. (C) Hexadecanal semicarbazone product ions. (D) Proposed pathways for product ion formation during (2E)-hexadecenal semicarbazone CID. cps, counts per second.

Molecular structure studies

Trzesowska [25] reported the molecular structure of *p*-dimethylaminobenzaldehyde semicarbazone (Figure 8.).

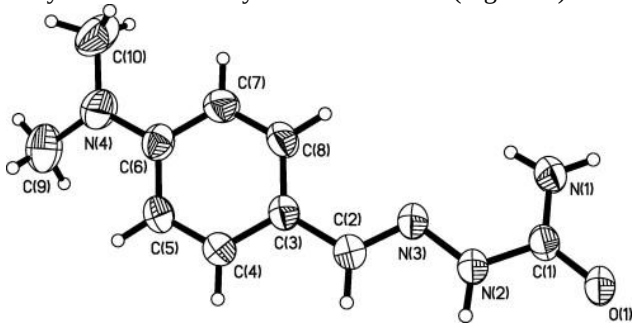
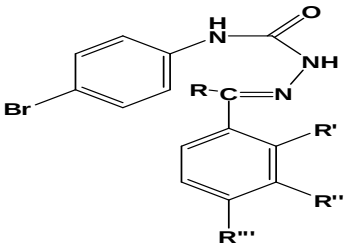


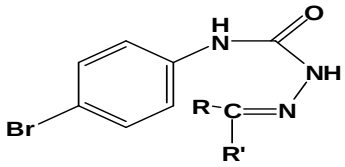
Fig. 8. The molecular structure of *p*-dimethylaminobenzaldehyde semicarbazone. The displacement ellipsoids are drawn at 50% probability level.

Anticonvulsant activity of Semicarbazones:

Pandeya *et al.* [10] synthesized a number of 4-bromophenyl semicarbazones (**1, 2**) and evaluated for anticonvulsant activity. After intraperitoneal injection to mice, the semicarbazone derivatives were examined in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole (scPTZ), subcutaneous strychnine (scSTY) and neurotoxicity (NT) screens. All the compounds showed anticonvulsant activity in one or more test models. A compound **2a** showed greatest activity, being active in all the screens with very low neurotoxicity. All the compounds except **1g** had lower neurotoxicity compared to phenytoin.



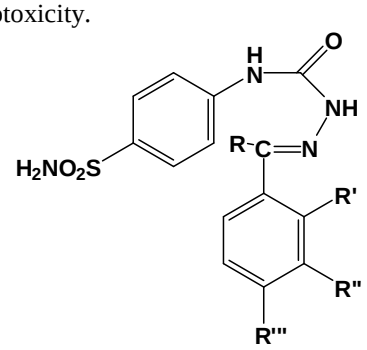
1



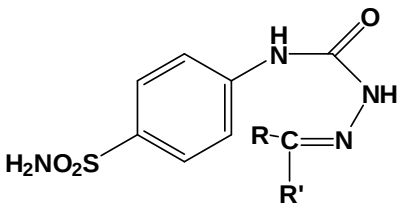
2

1a R’=Cl; R=R’’=R’’’=H
1b R’=NO_2; R=R’’=R’’’=H
2a R= R’=CH_3
1c R=R’=R’’=H; R’’’=$N(CH_3)_2$
2b R=H; R’=cinnamyl
1d R=R’=H; R’’= OCH_3; R’’’=OH
2c R=H; R’=piperanyl
1e R=R’=H; R’’=R’’’= OCH_3
2d R=H; R’=2-furyl
1f R= CH_3 ; R’=R’’=R’’’=H
2e R=R’=cyclohexanyl
1g R= CH_3 ; R’=R’’=H; R’’’= OH
2f R=R’= 2-CH_3-6-isopropyl cyclohexanyl

Yogeeswari *et al.* [32] synthesized a series of 4-sulphamoylphenyl semicarbazone derivatives (**3, 4**) starting from sulphanilamide and screened for anticonvulsant activity. The results indicated that greater protection was obtained in the maximal electroshock screen (MES) and subcutaneous strychnine (scSTY) than the subcutaneous pentylenetetrazole (scPTZ) tests. All the compounds showed low neurotoxicity when compared to the clinically used drugs. Compounds with substituted acetophenone (**3h-3k**) showed good activity in the rat oral MES screen. Seven compounds (**3f, 3h-3j, 3l, 4b** and **4c**) exhibited anticonvulsant activity greater than sodium valproate. Compound **3j** emerged as the most active compound as indicated by its protection in the MES and scSTY screens and with low neurotoxicity.



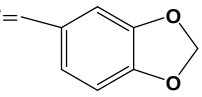
3



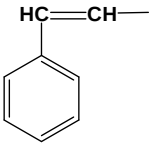
4

3a R= R’’= R’’’= H; R’= OH
3b R= R’’= R’’’= H; R’= Cl
3c R= R’’= R’’’= H; R’= NO_2
3d R= R’=R’’= H; R’’’= $N(CH_3)_2$
3e R= R’=R’’= H; R’’’= OCH_3
3f R= R’=H; R’’= OCH_3; R’’’= OH
3g R= R’=H; R’’= OCH_3; R’’’= OCH_3
3h R= CH_3; R’=R’’= R’’’= H
3i R= CH_3; R’=R’’= H; R’’’= OH
3j R= CH_3; R’=R’’= H; R’’’= CH_3
3k R= CH_3; R’=R’’= H; R’’’= NO_2
3l R= CH_3; R’=R’’= H; R’’’= NH_2

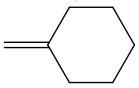
4a R= H; R'=



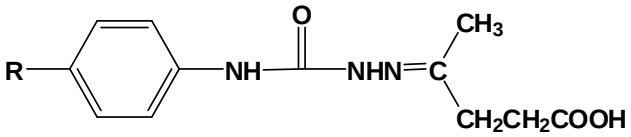
4b R=H; R'=



4c R=R'=



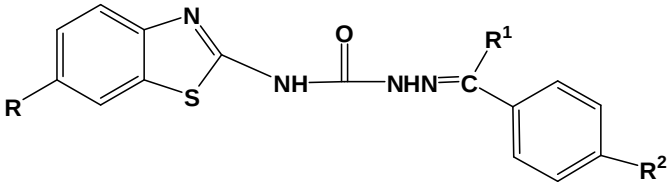
Aggarwal *et al.* [33] designed a series of 4-aryl substituted semicarbazones of levulinic acid **(5)** and synthesized to meet the structural requirements essential for anticonvulsant activity. All the compounds were evaluated for anticonvulsant activity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous metrazol (ScMet) induced seizure methods and minimal motor impairment was determined by rotorod test. A majority of the compounds exhibited significant anticonvulsant activity after intraperitoneal administration. 4-(4′-fluoro phenyl) levulinic acid semicarbazone emerged as the most active molecule, showing broad spectrum of activity with low neurotoxicity.



(5)

R=H, Cl, Br, F, CH_3, OCH_3, NO_2

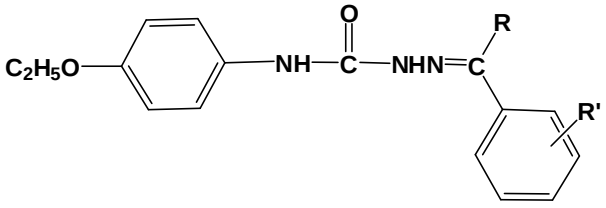
Siddiqui *et al.* [34] synthesized a series of 1,3-benzothizole-2-yl-semicarbazones **(6)** and evaluated for their anticonvulsant, neurotoxicity and other toxicity studies. Majority of the compounds were active in MES screens.



(6)

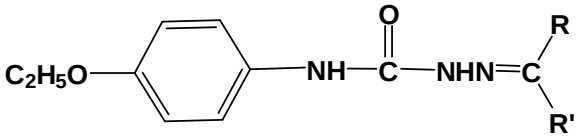
R=Cl, CH_3, OCH_3 ; R^1= CH_3, C_6H_5 ; R^2= H, OH, OCH_3, NO_2

Yogeeswari *et al.* [35] synthesized a series of 4-ethoxyphenyl semicarbazones **(7a), (7b)** and evaluated against MES and and ScPTZ induced seizure in mice. Among, the compound tested the compound with substituent showed protection from seizure in both animal models.



(7a)

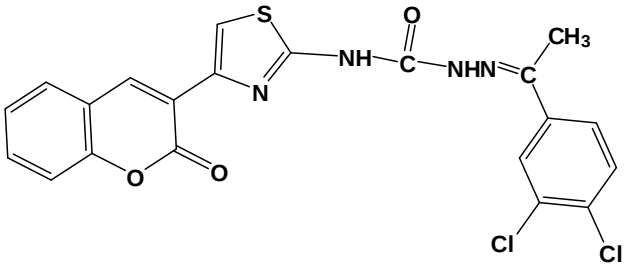
R= H, -CH_3 ; R'=2-Cl, 2-OH, 4-OH, 4-Cl



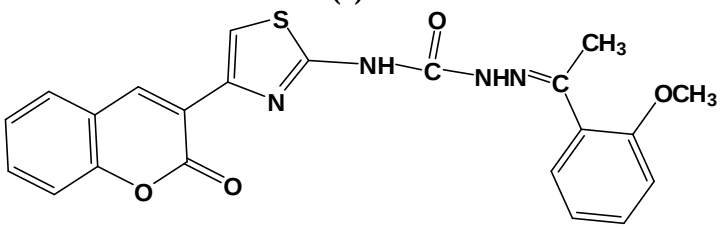
(7b)

R= -CH_3 ; R'= -CH_2COCH_3 , -$CH_2CH(CH_3)_2$

Siddiqui *et al.* [36] synthesized several heteroaryl semicarbazone by the reaction of heteroaryl hydrazine carboxamide with aryl aldehyde or ketone. Compounds were tested for anticonvulsant activity utilising PTZ and MES tests at 30, 100 and 300 mg/kg dose levels and found that (1E)-1-arylalkane-1-one-N-[4-(2-oxo-2H-chromen-2-yl)-1,3-thiazol-2-yl]semicarbazone **(8, 9,** and **10)** exhibited significant anticonvulsant activity at 30 mg/kg dose level comparable to the standard drug taken as phenytoin.



(8)



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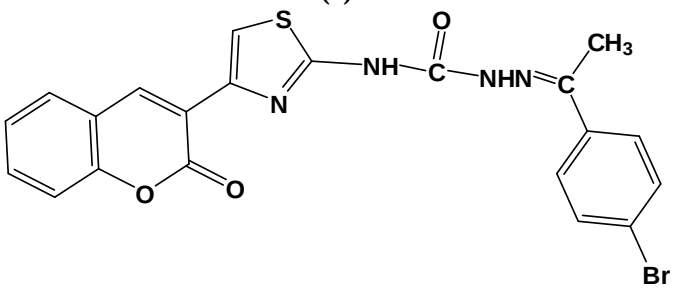
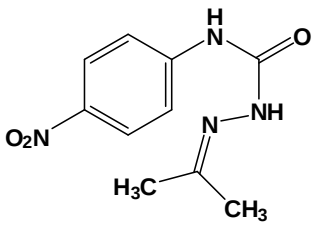
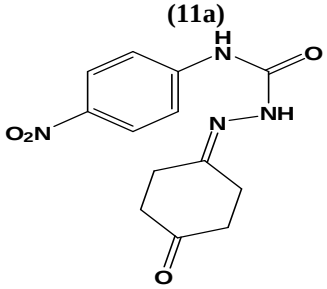


(10)

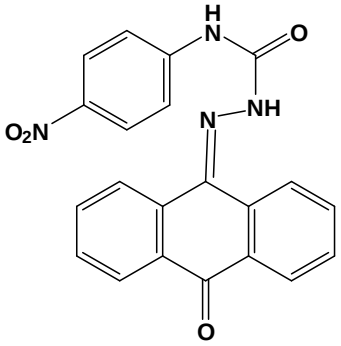
Pandeya *et al.* [37] synthesized a series of p-nitrophenyl substituted semicarbazones (**11a**-**c**) and phenoxy/p-bromophenoxy acetyl hydrazones (**12a**-**q**) were synthesized and their anticonvulsant activity was screened against maximal electroshock seizure (MES), subcutaneous metrazole (ScMet) and subcutaneous strychnine (ScSty) tests. Compounds **11a**-**c** with –NHCO– were found to be the most active in all these tests. These compounds were also active in the MES test after oral administration in rats.



(11a)



(11b)



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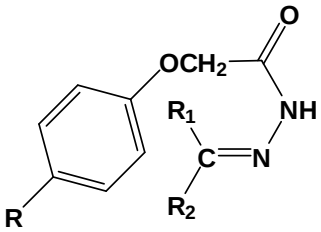
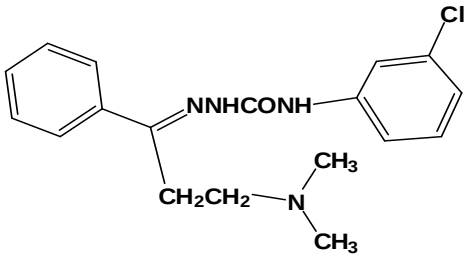


(12a-q)

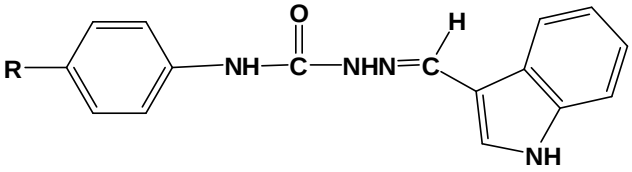
R= H, Br; R_1= H, CH_3; R_2=2-OH-C_6H_4, -C_6H_5, 4-OCH_3-C_6H_4, 2-Cl-C_6H_4, 4-Cl-C_6H_4, 4-NH_2-C_6H_4, 4-OH-C_6H_4, 4-$C_6H_5CH_2O$-C_6H_4 etc.

Raja *et al.* [38] designed and synthesized several semicarbazones of acetophenone and p- chloroacetophenone Mannich bases to meet the pharmacophore requirements essential for anticonvulsant activity. Mannich bases of acetophenone and *p*-chloroacetophenone were prepared by reacting formaldehyde with various secondary amines and then condensed with several aryl semicarbazides to yield the corresponding semicarbazones. All compounds were evaluated for their anticonvulsant activity by maximal electroshock (MES) and by subcutaneous metrazole (ScMet) and strychnine (ScSty) induced seizure methods, and their neurotoxic effects were determined using the rotorod test and found that 3-[3-chlorophenyl(β-dimethylaminopropiophenone)semicarbazone] **(13)** has excellent anticonvulsant activity in MES, ScSty, and ScMet tests.



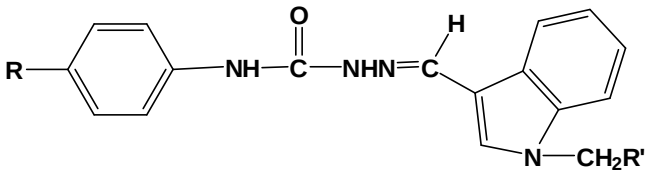
(13)

Srivastava *et al.* [39] prepared several indole derivatives **(14, 15)** by the reaction between indole-3- carboxaldehyde and various p-substituted phenylsemicarbazides, in the presence of glacial acetic acid. Later Mannich bases of indole derivatives were prepared by using formaldehyde & various secondary amines. The anticonvulsant activity of the synthesized compounds was evaluated by intraperitoneal administration in three seizure model which include isoniazid, thiosemicarbazide & 4-aminopyridine induced seizure. Some of the compounds were very much active against different anticonvulsant models.



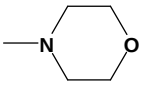
(14)

R=Cl, Br

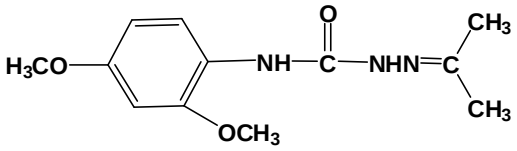


(15)

R=Cl, Br ; R'= $N(CH_3)_2$, $N(C_2H_5)_2$,

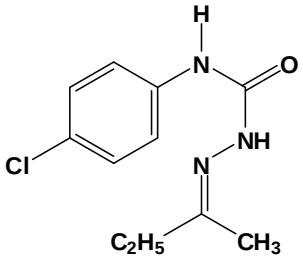


Thirumurugan *et al.* [40] synthesized 2,4-dimethoxyphenylsemicarbazones starting from 2,4-dimethoxyaniline via phenylcarbamate. The anticonvulsant activity of the synthesized compound were evaluated by intraperitoneal administration in three seizure model which include MES, Sc PTZ and Sc strychnine induced seizure. Most of the compounds exhibit protection in all three seizure model in which N^1-(2,4-dimethoxyphenyl)-N^4-(propan-2-one) semicarbazone **(16)** found to be most active with no neurotoxicity. The compound was also found to elevate *γ*-amino butyric acid (GABA) level in the mid brain and medulla oblongata region.



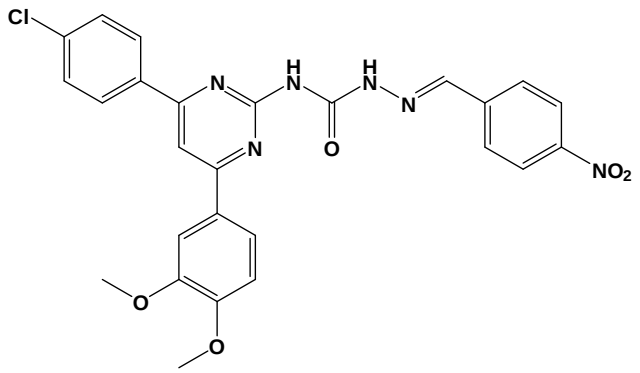
(16)

Singh *et al.* [41] synthesized a series of 4-(4-substituted aryl) semicarbazones from substituted anilines and evaluated for their anticonvulsant activities. The anticonvulsant activities were established by the anticonvulsant drug development (ADD) programme NIH, USA and screened against electroshock seizure, subcutaneous metrazole and minimal neurotoxicity tests. Compound **17** was found equipotent to carbamazepine in both MES and ScPTZ tests. This study has highlighted the importance of distal alkyl chain which influences the anticonvulsant activity.



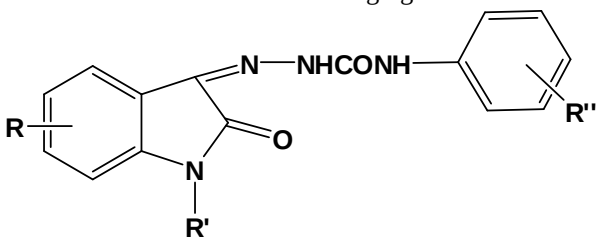
(17)

Alam *et al.* [42] synthesized a series of *N*-(4,6-substituted diphenylpyrimidin-2-yl) semicarbazones and tested for their anticonvulsant activity against the two seizure models, maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (scPTZ). Most of the compounds displayed good anticonvulsant activity with lesser neurotoxicity. The most active compound of the series was N^1-[4-(4-Chlorophenyl)-6-(3,4-dimethoxyphenyl)-pyrimidin-2-yl]- N^4-(4-nitrobenzaldehyde) semicarbazone **(18)** devoid of any neurotoxicity.

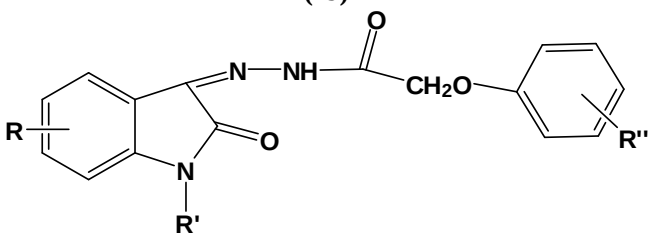


(18)

Pandeya *et al.* [43] synthesized a series of substituted isatin semicarbazones **(19, 20)** and all compounds were evaluated for their anticonvulsant activity by maximal electroshock seizure (MES), subcutaneous metrarazole (ScMet) and subcutaneous strychnine (ScSty) induced seizure models. A number of isatin semicarbazones exhibited significant protection after i.p. administration at the dose of 100 and 300 mg/kg. Some of them showed good anticonvulsant activity in MES test in rats after per oral administration at the dose of 30 mg/kg.



(19)



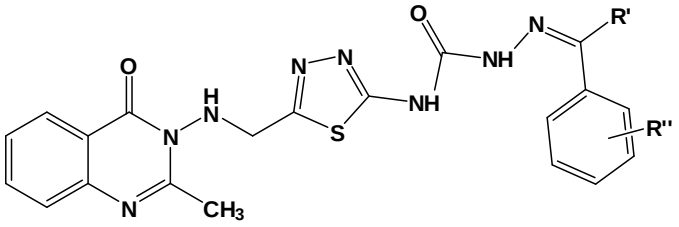
(20)

R=H, 4-Cl, 5-Cl, 6-Cl

R'=H, Acetyl, Benzyl

R''= 2-Cl, 4-Cl, 3-Cl, 4-Br, 4-SO_2NH_2, 4-NO_2

Rajak *et al.* [44] carried out synthesis of three novel series of semicarbazones containing 1,3,4-thiadiazole and quinazoline ring **(21)**. The anticonvulsant activities of the synthesized compound were evaluated by intraperitoneal administration in seizure model which include MES and ScPTZ induced seizure. The majority of the compounds were found active in the biological screening.

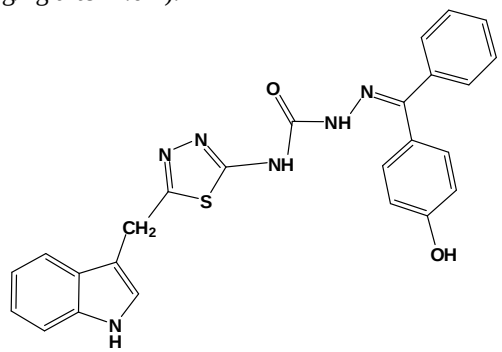


(21)

R'= H, C_6H_5, CH_3

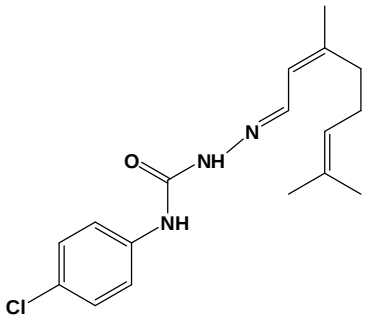
R''= H, 4-NO_2, 4-OH, 4-OCH_3, 4-CH_3, 4-Cl

Rajak *et al.* [45] synthesized a novel series of N^1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl}-N^4-(4-substituted benzaldehyde)-semicarbazones, N^1-{5-[(1*H*-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-substituted phenyl)ethanone]-semicarbazones and N^1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-substituted phenyl) (phenyl) methanone]-semicarbazones and evaluated for their anticonvulsant potential using maximal electroshock seizure (MES) and subcutaneous pentylenetrtrazole (*sc*PTZ) models. N^1-{5-[(1H-indol-3-ylmethyl)-1,3,4-thiadiazol-2-yl}-N^4-[1-(4-hydroxyphenyl) (phenyl) methanone]- semicarbazone **22** come out as the most active compound, showing considerable activity in maximal electroshock seizure (at 100 mg/kg after 0.5 h and at 300 mg/kg after 4.0 h) and subcutaneous pentylenetetrazole model (at 300 mg/kg after 4.0 h) without any neurotoxicity (up to 300 mg/kg after 4.0 h).

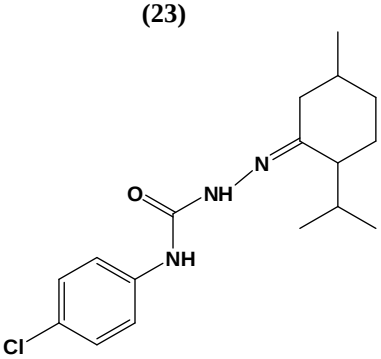


(22)

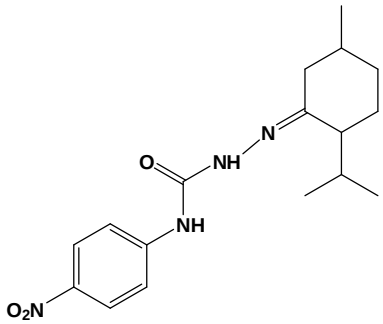
Khan *et al.* [46] synthesized a series of 4-aryl substituted semicarbazones of some terpenes i.e., citral (acyclic terpene), camphor (bicyclic terpene) and menthone (monocyclic terpene) from substituted anilines, to meet the structural requirements essential for anticonvulsant activity. The synthesized semicarbazone derivatives were evaluated for anticonvulsant activity by Isoniazid (INH) induced convulsion model, Thiosemicarbazide (TSC) induced convulsion model and 4-aminopyridine (4-AMP) induced convulsion model. All the compounds showed anticonvulsant activity in one or more test models. Compounds (**23, 24** and **25)** were found to be most active against INH screen at a dose of 30 mg kg^{-1} showed prolonged duration of action for 4 hours. Compound **25** showed prolong activity at a dose of 30 mg kg^{-1} against TSC screen. Compound **24** was found to be most potent anticonvulsant that showed activity in all screens with no neurotoxicity.



(23)

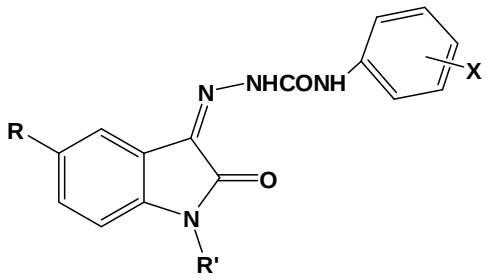


(24)



(25)

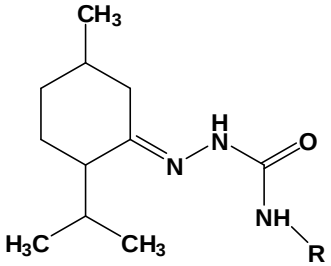
Smitha *et al.* [47] synthesized a series of *N*-methyl/acetyl 5-(un)-substituted isatin-3- semicarbazones **(26)** and screened for anticonvulsant activity. The results revealed that protection was obtained in all the screens i.e., Maximal electroshock, (MES) subcutaneous pentylene tetrazole (scPTZ) and subcutaneous strychnine (scSTY) screens. Among all the compounds compound with R=H, R'=$COCH_3$, X=4-Cl; R=H, R'=$COCH_3$, X=4-NO_2; and R=5-Br, R'=$COCH_3$, X=4-SO_2NH_2 emerged as broad-spectrum compounds as indicated by their protection in MES, scSTY and scPTZ screens.



(26)

R=H, 5-Br, R=5-NO_2; R'=$COCH_3$, CH_3;
X= H, 4-Cl, 4-NO_2, 2-Cl, 4-SO_2NH_2

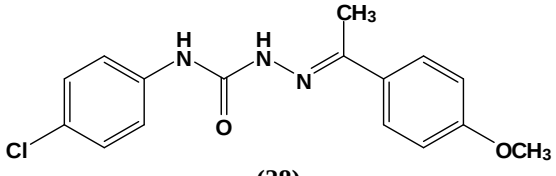
Verma *et al.* [48] synthesized a series of menthone semicarbazone **(27)** derivative and characterized by their spectral data and evaluated for anticonvulsant activity. Compounds showed significant anticonvulsant activity.



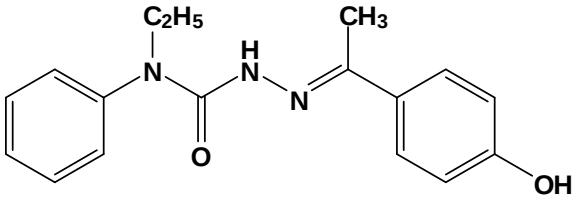
(27)

R= *p*-Br-C_6H_5, *p*-F-C_6H_5, *p*-NO_2-C_6H_5, C_5H_4N

Pandeya *et al.* [49] synthesized a series of 4-N-substituted arylsemicarbazones with increased lipophilicity and evaluated for anticonvulsant activity. The compounds provided significant protection against maximal electroshock induced seizures (MES) and seizures indicated by *sc* pentetrazole administration (*sc* PTZ) at 300 mg/kg after 0.5 h. The compounds **28** and **29** were active in MES and *sc* PTZ indicated seizure. The study has shown that introduction of alkyl (ethyl) at the terminal amino group and alkoxy (methoxy) moiety at the distal aryl ring led to increased activity and decreased toxicity.

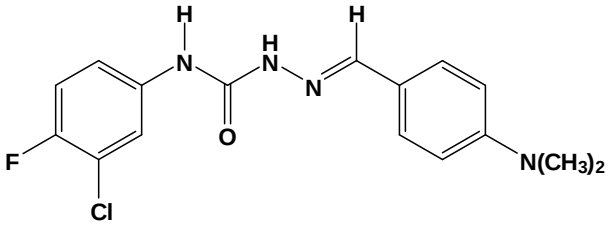


(28)



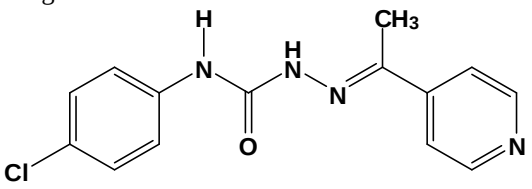
(29)

Amir *et al.* [50] synthesized several 3-chloro-4-florophenyl substituted semicarbazones. Some selected compounds have been evaluated for anticonvulsant activity by using maximal electroshock induced seizures (MES) test. N^1-(3-chloro-4-florophenyl)-N^4-(4-N,N-dimethylamino-benzaldehyde) semicarbazone **(30)** is found most active of the series without neurotoxicity.



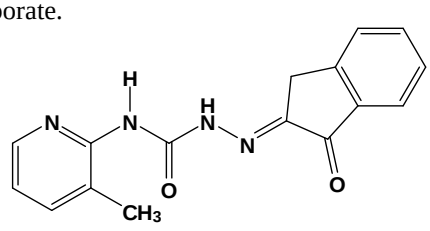
(30)

Aggarwal *et al.* [51] synthesized a series of 4-aryl substituted semicarbazones of pyridyl carboxaldehyde and pyridyl methyl ketone. All the compounds were evaluated for anticonvulsant activity and neurotoxicity. Anticonvulsant activity was determined after intraperitoneal (i.p.) administration to mice by maximal electroshock (MES) and subcutaneous metrazol (ScMet) induced seizure methods and minimal motor impairment was determined by rotorod test. Majority of compounds exhibited significant anticonvulsant activity after intraperitoneal administration. (Methyl-4-pyridyl) ketone-N_4-(*p*-chloro phenyl) substituted semicarbazone **(31)** emerged as most active derivative showing activity at 100 mg/kg in both the test with prolonged duration of action.



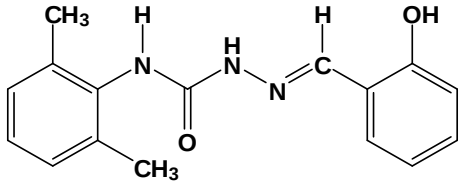
(31)

Yogeeswari *et al.* [52] synthesized a series of substituted *N*-(3-methylpyridin-2-yl) semicarbazones. All the compounds were evaluated for their anticonvulsant activity by maximal electroshock seizures (MES) test, subcutaneous pentylenetetrazole (scPTZ) screen, subcutaneous strychnine (scSTY) pattern test and subcutaneous picrotoxin (scPIC) seizure threshold test along with the behavioral, and neurotoxicity evaluation. A number of *N*-(3-methylpyridin-2-yl) semicarbazone derivatives exhibited significant protection after intraperitoneal administration at the dose of 100 and 300 mg/kg. Compound N^1-(3-methylpyridin-2-yl)-N^4-(isatin) semicarbazone **(32)** emerged as the most active analogue of the series, being more effective in most of the test models than ethosuximide and sodium valporate.



(32)

Yogeeswari *et al.* [53] synthesized various N^4-(2,6-dimethylphenyl) semicarbazones. All of the compounds exhibited anticonvulsant activity in the maximal electroshock test when administered by both intraperitoneal and oral routes. Compound N^1-(2,6-dimethylphenyl)-N^4-(2-hydroxybenzaldehyde) semicarbazone (**33**) emerged as a prototype with wide spectrum anticonvulsant agent active in five models of seizure with no neurotoxicity and hepatotoxicity. Compound **33** increased the 4-aminobutyric acid (GABA) level by 118% and inhibited the GABA transaminase enzyme both in vitro and ex vivo.



(33)

Conclusion:

The article has outlined the chemistry and anticonvulsant activity of the semicarbazones. The synthetic methodologies indicate the simplicity, maneuverability and versatility, which offer the medicinal chemist a complete range of novel derivatives. The high degree of protection against seizures can be positive signs for further investigation of semicarbazones as anticonvulsants. Semicarbazones are found to be a better target for the development of more and more anticonvulsant.

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